REMARKS

The present invention relates to compositions containing a drug coated with a protein, and methods for treating hyperplasia of non-cancerous cells, especially in a blood vessel, using such compositions. While the term "hyperplasia" may broadly embrace both cancerous and non-cancerous cells, the clear goal of the present disclosure, as reflected in the amended claims provided herewith, is treatment of non-cancerous cells, primarily in blood vessels.

By the present communication, claims 1, 9, 18, 25, 29 and 30 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. Entry of the amendments submitted herewith is submitted to be proper as the amendments place the present application in condition for allowance, or at a minimum, in better condition for appeal. Accordingly, entry of the proposed amendments is respectfully requested.

Upon entry of the amendments submitted herewith, claims 1, 3-18 and 20-30 will remain pending in this application. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2 of this communication.

Rejections under 35 U.S.C. §112, first paragraph

The withdrawal of the rejection of claims 1-16, 18-20 and 23-28 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, is acknowledged with appreciation.

The rejection of claims 1, 3-18 and 20-30 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that "[t]he claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention." (See the sentence bridging pages 2-3 of the Office Action).

Specifically, Applicants respectfully disagree with the Examiner's assertion that reference in the claims to "amorphous drug" allegedly lacks support in the present specification. (See the first full paragraph on page 3 of the Office Action). Contrary to the Examiner's assertion, "amorphous drug" is expressly recited in parent application US98/13272, for example, at page 27, lines 13-15 ('272 is incorporated by reference in the present application; see, for example, paragraph 50, line 7 of the present specification). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph are respectfully requested.

Rejection under 35 U.S.C. §102(e)

The rejection of claims 1, 6-8, 18 and 20-30 under 35 U.S.C. §102(e), as allegedly being anticipated by Desai et al. (U.S. Patent No. 5,916,596), is respectfully traversed. Applicants' invention, as defined, for example, by claim 1, distinguishes over Desai by requiring methods for treating hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof, employing compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein the drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Desai does not disclose such methods. Instead, Desai is directed to methods for preparation of substantially water insoluble pharmacologically active agents for in vivo delivery.

Applicants' invention, as defined, for example, by claim 18, further distinguishes over Desai by requiring compositions for treating hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof, said compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Desai does not disclose such compositions. Instead, Desai is directed to methods for preparation of substantially water insoluble pharmacologically active agents for in vivo delivery.

Applicants' invention, as defined, for example, by claim 25, further distinguishes over Desai by requiring compositions for reducing neointimal hyperplasia of non-cancerous cells in blood vessels associated with vascular interventional procedure(s), said compositions comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Desai does not disclose such compositions. Instead, Desai is directed to methods for preparation of substantially water insoluble pharmacologically active agents for in vivo delivery.

Applicants' invention, as defined, for example, by claim 29, still further distinguishes over Desai by requiring methods to reduce the toxicity of a drug that inhibits proliferation and migration of non-cancerous cells in a blood vessel, said methods comprising combining said drug, in amorphous form and in the form of nanoparticles, with a biocompatible protein, wherein said drug is coated with said protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Desai does not disclose such methods.

Applicants' invention, as defined, for example, by claim 30, still further distinguishes over Desai by requiring pharmaceutical formulations with reduced toxicity, said formulations comprising an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and migration of non-cancerous cells in a blood vessel, wherein said drug is coated with a biocompatible protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Desai does not disclose such formulations.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) are respectfully requested.

Rejections under 35 U.S.C. §103(a)

A. Grinstaff in view of Westesen

The rejection of claims 1, 6-8, 18 and 20-30 under 35 U.S.C. §103(a), as allegedly being unpatentable over Grinstaff et al. (U.S. Patent No. 5,498,421) in view of Westesen et al. (U.S. Patent No. 6,197,349), is respectfully traversed. Applicants' invention, as defined, for example, by claim 1, distinguishes over Grinstaff by requiring methods for treating hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof employing compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose or suggest such methods. Moreover, Grinstaff does not disclose or suggest any such compositions. Indeed, as acknowledged by the Examiner, "Grinstaff does not specify the drug form, i.e. instant amorphous form." (See page 5, line 3 of the Office Action; emphasis added). Only the present Applicants recognize the benefit of employing amorphous drug in the preparation of invention compositions and formulations; and only Applicants recognize the utility of such compositions and formulations for the treatment of hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof.

To the extent this rejection is based on the Examiner's observation that "the term hyperplasia includes cancer" (see page 4, line 25 of the Office Action), it is noted that the present claims, as amended herein, are directed specifically to the treatment of hyperplasia of non-

cancerous cells. As noted above, only the present Applicants recognize the benefit of employing amorphous drug in the preparation of invention compositions and formulations; and only Applicants recognize the utility of such compositions and formulations for the treatment of hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof.

Applicants' invention, as defined, for example, by claim 18, further distinguishes over Grinstaff by requiring compositions for treating hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof, said compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose or suggest such compositions.

Applicants' invention, as defined, for example, by claim 25, still further distinguishes over Grinstaff by requiring compositions for reducing neointimal hyperplasia of non-cancerous cells in blood vessels associated with vascular interventional procedure(s), said compositions comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose or suggest such compositions.

Applicants' invention, as defined, for example, by claim 29, still further distinguishes over Grinstaff by requiring methods to reduce the toxicity of a drug that inhibits proliferation and migration of non-cancerous cells in a blood vessel, said methods comprising combining said drug, in amorphous form and in the form of nanoparticles, with a biocompatible protein, wherein said drug is coated with said protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose or suggest such methods.

Applicants' invention, as defined, for example, by claim 30, still further distinguishes over Grinstaff by requiring pharmaceutical formulations with reduced toxicity, said formulations comprising an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and migration of non-cancerous cells in a blood vessel, wherein said drug is coated with a biocompatible protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Grinstaff does not disclose or suggest such formulations.

Further reliance on Westesen is unable to cure the deficiencies of Grinstaff. Westesen is directed to particles comprising a supercooled melt of a poorly soluble substance and a stabilizing agent. As readily recognized by those of skill in the art, particles of supercooled melts are very different in size, shape and composition from the particles disclosed by Grinstaff, or the nanoparticles contemplated by the present claims. Furthermore, to work with melts of a poorly soluble substance, one would, of necessity, have to work at temperatures sufficient to achieve a melt, which elevated temperatures would clearly be incompatible with delicate structures such as the biocompatible protein employed in the preparation of invention compositions and formulations. As a result, one attempting to combine the teachings of the asserted references would achieve a very different article than contemplated by the present claims.

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) are respectfully requested.

B. Kunz in view of Westesen

The rejection of claims 1, 3-18 and 20-30 under 35 U.S.C. §103(a), as allegedly being unpatentable over Kunz et al. (U.S. Patent No. 5,733,925) in view of Westesen et al., is respectfully traversed. Applicants' invention, as defined, for example, by claim 1, distinguishes over Kunz by requiring methods for treating hyperplasia (especially hyperplasia of non-cancerous cells in blood vessels) in a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such methods. Instead, Kunz contemplates use of drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 5, distinguishes over Kunz by requiring methods for treating hyperplasia (especially hyperplasia of non-cancerous cells in a blood vessel) in a subject in need thereof, said method comprising administering to said subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof, wherein the effective amount falls in the range of about 0.01 mg/kg up to about 15 mg/kg for a human subject, and wherein said administration of said composition is repeated over a dosing cycle between 1 day and 6 months.

Kunz does not disclose or suggest such methods. Instead, Kunz contemplates methods which use drug conjugated with a binding protein. Thus, Kunz requires a chemical modification

of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 9, further distinguishes over Kunz by requiring methods for reducing neointimal hyperplasia of non-cancerous cells associated with vascular interventional procedure(s) in a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such methods. Instead, Kunz contemplates use of drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 14, further distinguishes over Kunz by requiring methods for reducing neointimal hyperplasia of non-cancerous cells associated with vascular interventional procedure(s) in a subject in need thereof, said method comprising administering to said subject an effective amount of a composition comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof, wherein said effective amount falls in the range of about 0.01 mg/kg up to about 15 mg/kg for a human subject, and wherein said administration of said composition is repeated over a dosing cycle between 1 day and 6 months.

Kunz does not disclose or suggest such methods.

Applicants' invention, as defined, for example, by claim 16, still further distinguishes over Kunz by requiring methods for reducing neointimal hyperplasia of non-cancerous cells

associated with vascular interventional procedure(s) in a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof, wherein said composition is administered by deployment of a stent containing said at least one drug coated thereon.

Kunz does not disclose or suggest such methods.

Applicants' invention, as defined, for example, by claim 17, still further distinguishes over Kunz by requiring methods to reduce proliferation and migration of non-cancerous cells in a blood vessel of a subject undergoing a vascular interventional procedure, said methods comprising systemically administering to said subject before, during or after said procedure, a formulation comprising (i) an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and cell migration, and (ii) a biocompatible protein wherein said drug is coated with said protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such methods. Instead, Kunz contemplates use of drug conjugated with a binding protein. Thus, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 18, further distinguishes over Kunz by requiring compositions for treating hyperplasia of non-cancerous cells in a blood vessel of a subject in need thereof, said compositions comprising (i) at least one amorphous drug in nanoparticle form, and (ii) protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such compositions. Instead, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 22, still further distinguishes over Kunz by requiring compositions for treatment of hyperplasia (especially hyperplasia of non-cancerous cells ina blood vessel), said compositions comprising (i) amorphous paclitaxel in nanoparticle form, and (ii) protein.

Kunz does not disclose or suggest such compositions.

Applicants' invention, as defined, for example, by claim 25, further distinguishes over Kunz by requiring compositions for reducing neointimal hyperplasia of non-cancerous cells in blood vessels associated with vascular interventional procedure(s), said compositions comprising at least one amorphous drug in nanoparticle form, coated with a protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such compositions.

Applicants' invention, as defined, for example, by claim 29, still further distinguishes over Kunz by requiring methods to reduce the toxicity of a drug that inhibits proliferation and migration of non-cancerous cells in a blood vessel, said methods comprising combining said drug, in amorphous form and in the form of nanoparticles, with a biocompatible protein, wherein said drug is coated with said protein, wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such methods. Instead, Kunz requires a chemical modification of drug by conjugation thereto with a binding protein, rather than the much simpler physical process of coating drug with protein, as contemplated by the present claims.

Applicants' invention, as defined, for example, by claim 30, still further distinguishes over Kunz by requiring pharmaceutical formulations with reduced toxicity, said formulations comprising an amorphous drug in nanoparticle form, wherein said drug inhibits proliferation and migration of non-cancerous cells in a blood vessel, wherein said drug is coated with a biocompatible protein, and wherein said drug is selected from the group consisting of an antineoplastic, an antiproliferative, an angiogenesis inhibitor, and mixtures of any two or more thereof.

Kunz does not disclose or suggest such formulations.

Further reliance on Westesen is unable to cure the deficiencies of Kunz. As discussed above, Westesen is directed to particles comprising a supercooled melt of a poorly soluble substance and a stabilizing agent. As readily recognized by those of skill in the art, particles of supercooled melts are very different in size, shape and composition from the particles disclosed by Kunz, or the nanoparticles contemplated by the present claims. Furthermore, to work with melts of a poorly soluble substance, one would, of necessity, have to work at temperatures sufficient to achieve a melt, which elevated temperatures would clearly be incompatible with delicate structures such as the biocompatible protein employed in the preparation of invention compositions and formulations. As a result, one attempting to combine the teachings of the asserted references would achieve a very different article than contemplated by the present claims.

Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) are respectfully requested.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: May 3, 2005

By: _____

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